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Cystatin C and Sudden Cardiac Death Risk in the Elderly

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Abstract

Background—Recent studies have demonstrated an association between moderate kidney dysfunction and sudden cardiac death in people with cardiovascular disease.

Methods and Results—The study was a longitudinal analysis among 4465 participants from the Cardiovascular Health Study without prevalent cardiovascular disease at baseline. Cystatin C and creatinine were measured from baseline sera. SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual that occurred out of the hospital or in the emergency room. The association between cystatin C tertiles and SCD was determined with multivariate Cox proportional hazards. A similar analysis compared SCD incidence across creatinine-based eGFR tertiles. Over a median follow-up of 11.2 years, 91 adjudicated SCD events occurred. The annual incidence of SCD events increased across cystatin C tertiles: 10 events per 10,000 person years in tertile 1, 25 events per 10,000 person years in tertile 2 and 32 events per 10,000 person years in the highest cystatin C tertile. These associations persisted after multivariate adjustment: [HR = 2.72, 95% CI (1.44–5.16) in tertile 2 and HR = 2.67, 95% CI (1.33–5.35) in tertile 3]. After multivariate adjustment, the rate of SCD also increased in a linear distribution across creatinine-based eGFR tertiles: 15 events per 10,000 person years in tertile 1, 22 events per 10,000 person years in tertile 2

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and 27 events per 10,000 person years in tertile 3. No significant associations, however, remained between creatinine-based eGFR and SCD after multivariable adjustment.

Conclusion—Impaired kidney function, as measured by cystatin C, has an independent association with SCD risk among elderly persons without clinical cardiovascular disease.

Keywords

Cystatin C; kidney; sudden cardiac death; epidemiology

Introduction

Sudden cardiac death (SCD) is an important clinical and public health problem with over 450,000 Americans dying annually from this condition.¹ Observational and post-mortem data indicate that coronary arterial abnormalities and their consequences are the cause of 80% of fatal arrhythmias. The presence and severity of underlying heart disease including coronary heart disease, chronic heart failure, and depressed left ventricular ejection fraction, are the most predictive risk factors for the future occurrence of SCD.^{2–6} In addition, population-based studies have demonstrated an association between traditional coronary heart disease risk factors including dyslipidemia, hypertension, cigarette smoking, physical inactivity, obesity, and a family history of premature coronary heart disease and SCD.^{7–12} Another population at high risk for SCD are persons with end-stage renal disease (ESRD).⁵ According to the US Renal Data System, about 22% of all deaths in persons with ESRD are caused by SCD, and the incidence increases with age: 2% per year for ages 20 to 44 years, 3.7% per year for ages 45 to 64 years, and 7% per year for ages 65 years and older.^{5, 13}

Recent observational studies have demonstrated an association between moderate kidney dysfunction and SCD risk in people with cardiovascular disease.^{14–17} The majority of these participants had a history of myocardial infarction and congestive heart failure; as a result, it is difficult to know whether chronic kidney dysfunction was merely a marker of cardiovascular disease or an independent predictor of risk. As a result, we sought to evaluate whether impaired kidney function predicts SCD events among people in the community without cardiovascular disease. We hypothesized that impaired kidney function measured using creatinine-based estimated glomerular filtration rate (eGFR) and cystatin C would have an independent association with SCD incidence. We investigated this hypothesis among elderly participants in the Cardiovascular Health Study (CHS) without prevalent cardiovascular disease.

Methods

Design

The CHS¹⁸ is a community-based study of cardiovascular disease risk in ambulatory elderly persons, sponsored by the National Institute of Health. This analysis evaluates the longitudinal association between baseline kidney function and subsequent sudden cardiac death events.

Study Population

The CHS recruited participants from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. Recruiting participants from these four US communities allowed for a mixture of urban and rural populations and adequate numbers of both men and women. To be eligible, persons had to be at least 65 years of age, not institutionalized, expected to remain in the current community for three years or longer, not under active treatment for cancer, and able to provide written informed consent. The initial 5201 participants were enrolled from January 1989 to June 1990; an additional 687 black participants (with race self-reported) were recruited

1992–1993 and enrolled by June 1993. This analysis excluded those persons with prevalent clinical cardiovascular disease, defined as a history of MI or CHF, at entry into the cohort. There remained 4482 participants with baseline measures of kidney function. Missing data constituted 0.4% of the data leaving a sample size of 4465 participants for this project. All participants provided written informed consent, and the institutional review boards at all participating sites approved the study protocol.

Participants underwent a comprehensive examination at baseline, which included a thorough medical history, physical examination, laboratory testing, a 12-lead ECG, and assessment of cardiovascular disease status. Of the participants in this study, 3887 had a baseline transthoracic echocardiographic study to evaluate for left ventricular ejection fraction. The study design, quality-control procedures, laboratory methods, and procedures for blood-pressure measurement have been published previously.^{18, 19}

Sudden cardiac death

Sudden cardiac death (SCD) was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual occurring out of the hospital or in the emergency room. These cases could not have life-threatening, noncardiac comorbidities or be under hospice or nursing home care. SCD cases were identified and adjudicated by a cardiologist's record review of all cardiac deaths; survivors or successfully resuscitated events were not included in the definition of SCD. A second physician conducted blind review of a sample of 70 potential cases with an 88% inter-reviewer agreement and kappa value of 0.74 for SCD.²⁰

Kidney Function Assays

Measurements were performed on fasting sera specimens that had been stored at -70 degrees Celsius. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).²¹ The assay range is 0.195 to 7.330 mg/L, with the reference range for young, healthy individuals reported as 0.53–0.95 mg/L. The assay was demonstrated to remain stable over 5 cycles of freeze/thaw without change in the measurement.^{21, 22}

Serum creatinine was assayed by a colorimetric method (Ektachem 700, Eastman Kodak). The mean coefficient of variation for monthly controls was 1.94 percent (range, 1.16 to 3.90). We estimated the creatinine-based GFR with the use of the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation.²³ Prior to estimating the GFR, creatinine levels were indirectly calibrated to the Cleveland Clinic lab as previously described.²⁴

Cystatin C and creatinine-based eGFR were categorized into tertiles in order to maintain an equal distribution of participants across kidney function measures and to ensure a sufficient number of SCD events within each group. We also calculated a cystatin C-based eGFR for each cystatin C tertile using a recently derived and validated equation.²⁵ We then defined a subset of participants with preclinical kidney disease using both cystatin C and creatinine-based eGFR measurements. The three groups included the following: chronic kidney disease (eGFR < 60 ml/min/1.73m²), preclinical kidney disease (eGFR > 60 ml/min/1.73m² and cystatin C > 1.0 mg/L) and normal kidney function (eGFR > 60 ml/min/1.73m² and cystatin C < 1.0 mg/L) as in prior studies.²⁶

Statistical Methods

Baseline characteristics of participants were compared across cystatin C tertiles using chi-squared or ANOVA tests. The association between cystatin C and SCD was determined with multivariate Cox proportional hazards regression models that compared each ascending tertile

of cystatin C with the lowest one. A similar evaluation was performed to determine the association between creatinine-based eGFR tertiles and SCD. In these multivariate models, candidate variables for adjustment were retained in the final models if they changed the beta coefficient of the primary predictor of interest (kidney function) by at least 5 percent. In addition, we adjusted for covariates that are known to be associated with sudden cardiac death.

Covariates were selected as candidates for multivariate analysis based on their potential to confound the association of kidney function with SCD or for their independent association with SCD based on prior studies. Specifically, the following variables from table 1 changed the coefficient of cystatin C by at least 5% and were included in the multivariate analysis: diabetes, systolic blood pressure, diastolic blood pressure, LVH, calcium channel blockers, diuretics and aspirin use. In addition age, gender and race (self-reported) were forced into the multivariate models. Finally, current smoking, measures of dyslipidemia including LDL and HDL, body mass index, alcohol use, a family history of cardiovascular disease and physical activity are variables known to be associated with SCD and were included in the multivariate analysis.^{7, 8, 11, 12, 27} Other baseline variables such as ECG metrics and medications including ACE inhibitors, beta blockers, diuretics, calcium channel blockers, digitalis, and statins were not included in the multivariate model as they did not effect the association between kidney dysfunction and SCD. Incident MI and CHF were analyzed as time-dependent covariates in the multivariate analysis. Additional adjustment for left ventricular ejection fraction was performed to evaluate SCD risk among those participants who had baseline echocardiograms.

The proportional hazards assumption was not violated in any of these analyses. Model predictiveness was evaluated using the c-statistic. Bootstrapping methods were also implemented to evaluate over-fitting of the data. S-Plus (release 6.1, Insightful Inc, Seattle, WA) and SPSS statistical software (release 15.0, SPSS Inc, Chicago, IL) were used for the analyses. A P value <0.05 was considered statistically significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Participants in the highest cystatin C tertile were on average older and more likely to be male and white instead of black (table 1). In addition, they had higher BMI, higher systolic blood pressure, a lower HDL and were more likely to have a history of hypertension, diabetes, atrial fibrillation and left ventricular hypertrophy (LVH). Participants with higher cystatin C were more likely to be on ACE inhibitors, diuretics, beta blockers, calcium channel blockers, digitalis and aspirin. They also had a higher likelihood of having a family history of cardiovascular disease. Creatinine levels increased and eGFR decreased across cystatin C tertiles. Participants in the highest cystatin C tertile had a mean creatinine-based eGFR of 63 ml/min/1.73m². Finally, nearly all participants had normal left ventricular ejection fraction as assessed by transthoracic echocardiography.

SCD Incidence

Among the 4465 subjects, 91 adjudicated SCD events occurred over a median follow-up of 11.2 years. The incidence of SCD events increased across cystatin C tertiles: 0.10% (per year), 0.25%, and 0.32% (figure 1). An increase in SCD risk was also observed across creatinine-based eGFR tertiles: 0.15%/year, 0.22%/year, and 0.27%/year. SCD risk remained increased in those with elevated cystatin C concentrations in both unadjusted and adjusted analysis. The

risk for SCD increased more than 3-fold across cystatin C tertiles in unadjusted analysis (table 2). After adjusting for multiple variables including incident CHF and MI, cystatin C tertiles retained an independent risk of SCD. In addition, among the 3887 participants with baseline echocardiograms, cystatin C remained an independent predictor of SCD after adding left ventricular ejection fraction to the multivariate model: [HR = 3.25, 95% CI (1.54–6.85) in tertile 2; HR = 2.82, 95% CI (1.26–6.32) in tertile 3]. Finally, only the highest creatinine-based eGFR tertile was predictive of SCD risk in unadjusted analysis; however, it did not achieve statistical significance after multivariate adjustment (table 3).

To assess the predictiveness of this model, the c-statistic was applied to a fully adjusted model with and without cystatin C. There was a significant improvement upon adding cystatin C to the fully adjusted model ($p=0.002$) with a c-statistic of 0.6735 (fully adjusted) versus 0.6847 (with the addition of cystatin C). In addition, bootstrapping of the fully adjusted Cox model was performed to assess over-fitting of the data. A histogram of the mean deviance residuals from the resultant bootstrapped sample centered on the vertical line indicates that the model behaves well. Further, the bootstrap estimates (using 100 re-samples) indicate that the model was not over-fitted (original Somer's D = -0.37 versus corrected Somer's D = -0.35).

SCD risk among those with preclinical kidney disease

After excluding persons with CKD (creatinine-based eGFR < 60 ml/min/1.73m²), participants with preclinical kidney disease (creatinine-based eGFR ≥ 60 ml/min/1.73m² and cystatin C ≥ 1.0 mg/L) had a two-fold SCD risk compared to those without CKD and low cystatin C concentrations [HR 2.68, 95% CI (1.53 – 4.69) in unadjusted analysis and HR 1.99, 95% CI (1.11 – 3.57) after multivariate adjustment]. This risk increase was similar to that of CKD compared with the normal kidney function (creatinine-based eGFR ≥ 60 mL/min/1.73m² and cystatin C < 1.0 mg/L) referent group (HR=2.37; 95% CI, 1.41 to 3.98 in unadjusted analysis and HR=2.09; 95% CI, 1.21 to 3.61 after multivariate adjustment).

Discussion

In this community-based study of ambulatory older adults, impaired kidney function was associated with increased risk of SCD. There was an increased SCD risk among those participants with elevated cystatin C concentrations after multivariate analysis including adjustment for left ventricular ejection fraction. This elevated risk is similar in the second and third cystatin C tertiles. Whether tertile 1 is protective or tertiles 2 and 3 are at greater risk is difficult to distinguish. The cystatin C levels in tertile 2 (0.92 – 1.09 mg/L), however, would generally be considered abnormal and likely reflect the adverse cardiovascular consequences of impaired kidney function. Interestingly, participants meeting the definition of “preclinical kidney disease” had elevated risks of SCD that were equivalent to participants with CKD.

These findings extend the range of adverse cardiovascular events associated with elevated cystatin C concentrations also to include sudden cardiac death. Prior studies have demonstrated an independent association between elevated cystatin C concentrations and both cardiovascular and non-cardiovascular mortality.^{22, 26, 28} The spontaneous nature of SCD events, however, suggests a distinct process from other types of cardiovascular death where long-standing symptoms associated with pump failure and ischemia are often present. In addition the adjudication for SCD focused on people who were not hospitalized, which distinguishes it from all other cardiovascular events. Further, we excluded participants with prevalent cardiovascular disease to enhance the specificity for identifying arrhythmic events such as ventricular tachycardia or ventricular fibrillation. To further minimize the confounding effects of cardiovascular disease, we also adjusted for incident myocardial infarction and congestive heart failure. Finally, these findings extend the association of kidney dysfunction and sudden cardiac death risk to the setting of preclinical kidney disease. Previous studies have

demonstrated an association between end stage and chronic kidney disease to SCD^{15–17} especially in patients with advanced heart failure and coronary disease. Even mild kidney dysfunction is associated with a range of adverse cardiovascular events including SCD.

Several findings from our study also suggest that SCD may be a direct result of kidney dysfunction. The temporal association between kidney disease and SCD in this cohort study suggests that it may be a causal one. The increased risk of SCD observed in this study may have been attributable to higher rates of malignant ventricular arrhythmias.²⁹ Prior studies have demonstrated the increased prevalence of left ventricular hypertrophy, systolic dysfunction and diastolic dysfunction among patients with kidney disease including those with elevated cystatin C concentrations.³⁰ Though we adjusted for LVH and systolic dysfunction, other structural changes may be present in the absence of clinical heart failure and may contribute to greater cardiac fibrosis and arrhythmia risk.^{30, 31} In addition, autonomic dysfunction, myocyte dysfunction and altered electrolyte metabolism may contribute to arrhythmic risk in patients with kidney dysfunction.^{32–34}

Our findings suggest that cystatin C levels and the corresponding cystatin-based eGFR provide a stronger estimate of the risk of sudden cardiac death among elderly persons than creatinine-based estimates. Creatinine is an insensitive measure of kidney function in elderly persons among whom lean muscle mass comprises a smaller and unpredictable proportion of body mass. Prior studies have also demonstrated that cystatin C levels are superior to creatinine and creatinine-based estimates of GFR for predicting adverse cardiovascular events among elderly individuals.²² In this analysis, we also found cystatin C to have a linear association with the risk of sudden cardiac death. This finding contrasts with traditional measures of renal function where the risk of adverse events increased only when GFR dropped below a threshold of 60 ml per minute per 1.73 m² of body-surface area.^{35–37} Cystatin C is most likely a stronger predictor of adverse cardiovascular events in the elderly because it provides a better approximation of GFR across the spectrum of kidney function.

Elevated cystatin C concentrations also capture a state of preclinical kidney disease that is highly prevalent among this population-based cohort of ambulatory, elderly persons. A preclinical state refers to a specific condition that precedes the development of overt, clinical disease. Preclinical disease states have been associated with adverse health consequences;^{26, 38–42} therefore, their identification can have important clinical consequences. Participants in our study without chronic kidney disease (estimated GFR ≥ 60 ml/min per 1.73m²) and elevated cystatin C levels were at substantially increased risk for sudden cardiac death events during the follow-up period. Whether kidney disease is labeled as preclinical or undetected, elevated cystatin C concentrations were independently associated with sudden cardiac death events among participants without chronic kidney disease. Because an estimated GFR less than 60 ml/min per 1.73 m² seems specific for defining abnormal kidney function in elderly persons, we believe it remains the appropriate initial screening measure for kidney dysfunction. Measuring cystatin C concentrations in persons with an estimated GFR greater than 60 mL/min per 1.73 m² may be a useful test for further defining kidney function and for distinguishing levels of cardiovascular risk.

Several limitations of the current study should be considered. Since CHS consisted solely of elderly persons, the described associations of cystatin C with SCD cannot necessarily be extrapolated to younger populations. In addition, as with any observational study, there is likely to be residual confounding in the association of cystatin C with SCD. For example, a variety of unmeasured factors might modify the associations between higher cystatin C concentrations and sudden death. Finally, this study cannot distinguish the extent to which the observed associations of cystatin C with SCD reflect its approximation of GFR versus a direct or indirect pathologic link from cystatin C to cardiovascular risk that is independent of kidney function.

The findings from our study provide insight that SCD may be related to impaired kidney function. These results suggest that even mild reductions in kidney function, evidenced by higher cystatin C levels, can alter the electrophysiologic properties of the myocardium and increase the risk for SCD, without any clinical evidence of CHF, coronary disease or cardiac structure. Future studies should investigate candidate mechanisms to explain the SCD risk of mild to moderate kidney dysfunction.

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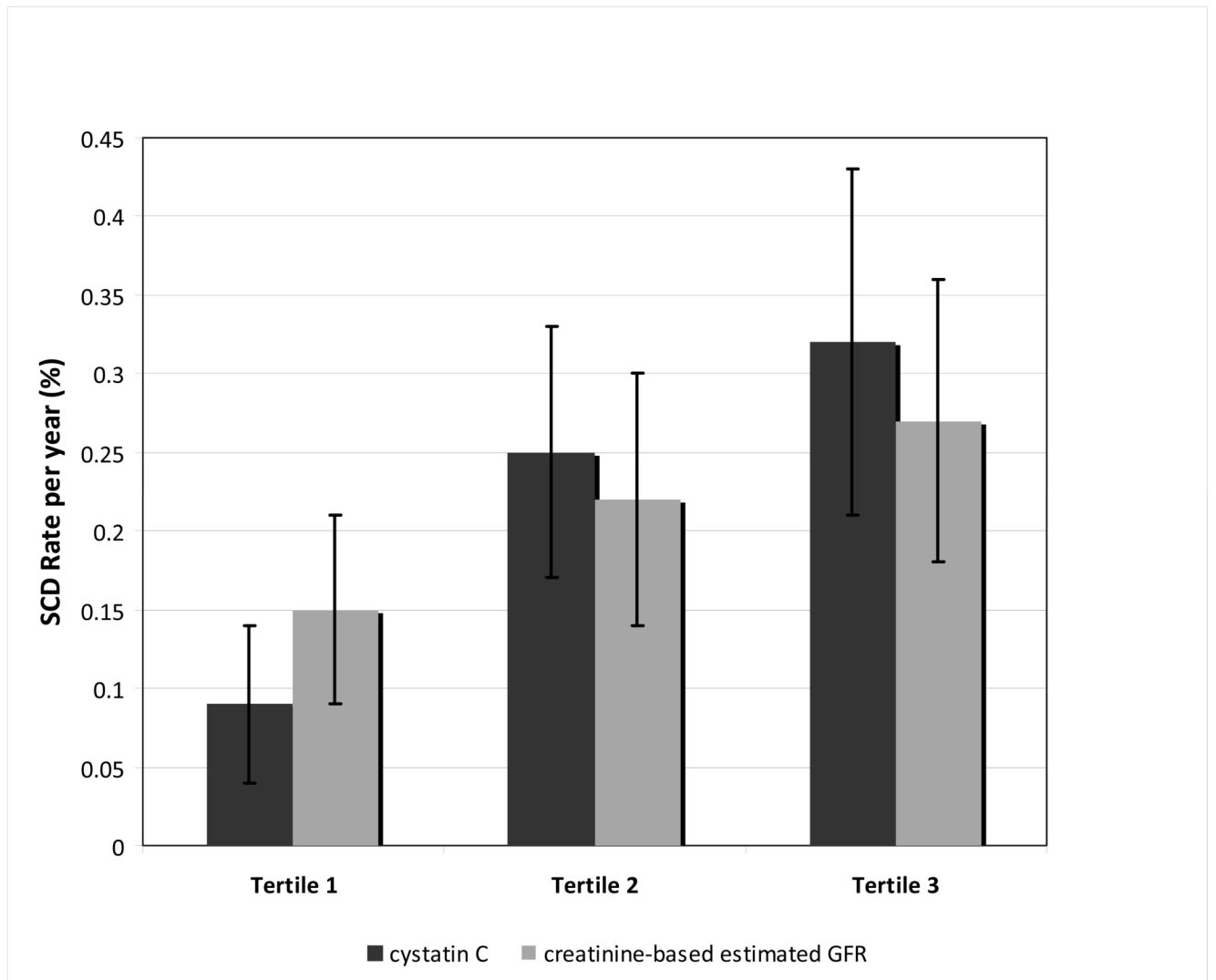


Figure 1. Sudden cardiac death rate per year
x-axis: cystatin C and creatinine-based estimated GFR tertiles
y-axis: sudden cardiac death rates per year (% per year)

Table 1

Baseline characteristics across Cystatin C Tertiles

	Cystatin C Tertiles			p-value (trend)
	≤ 0.91 mg/L	0.92–1.09 mg/L	≥1.10 mg/L	
N	1579	1582	1304	
Age (yr; mean ± SD)	71 ± 4	72 ± 5	75 ± 6	<0.001
Men (n [%])	479 (30)	605 (38)	549 (42)	<0.001
Black (n [%])	297 (19)	239 (15)	198 (15)	0.006
Smoking				0.011
Former (n [%])	656 (42)	615 (39)	519 (40)	
Current (n [%])	158 (10)	205 (13)	188 (14)	
Alcohol use (beverages/wk; median [interquartile range])	0.04 [0, 2.00]	0.02 [0, 1.25]	0 [0, 0.75]	<0.001
BMI (kg/m ² ; mean ± SD)	25.9 ± 4.2	26.8 ± 4.8	27.6 ± 5.1	<0.001
Physical activity (Kcal/wk; median [interquartile range])	1238 [489, 2528]	1134 [438, 2446]	810 [270, 1835]	<0.001
SBP (mmHg; mean ± SD)	134 ± 21	135 ± 21	139 ± 22	<0.001
DBP (mmHg; mean ± SD)	71 ± 11	71 ± 11	71 ± 12	0.755
Hypertension (n [%])	809 (51)	869 (55)	927 (71)	<0.001
Diabetes (n [%])	214 (14)	203 (13)	221 (17)	0.027
Potassium (mMol/dl; mean ± SD)	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	<0.001
LDL (mg/dl; mean ± SD)	130 ± 34	132 ± 36	130 ± 37	0.541
HDL (mg/dl; mean ± SD)	60 ± 16	55 ± 15	51 ± 15	<0.001
Family history of CV (n [%])	431 (27)	449 (28)	394 (30)	0.073
Electrocardiographic Metrics				
AF (n [%])	14 (1)	29 (2)	42 (3)	<0.001
LVH	54 (3)	40 (3)	79 (6)	0.001
QT interval (msec; mean ± SD)	416 ± 32	415 ± 34	414 ± 38	0.232
LBBB (n [%])	20 (1)	22 (1)	24 (2)	0.212
Medications				
ACE-I (n [%])	79 (5)	94 (6)	117 (9)	<0.001
Diuretics (n [%])	302 (19)	377 (24)	534 (41)	<0.001
B-blockers (n [%])	137 (9)	166 (10)	218 (17)	<0.001
Calcium-channel blockers (n [%])	161 (10)	158 (10)	169 (13)	0.029
Aspirin (n [%])	37 (2)	37 (2)	50 (4)	0.047
Statins (n [%])	48 (3)	26 (2)	20 (2)	0.005
Measures of kidney function				
Cystatin C (mg/L; mean ± SD)	0.81 ± 0.07	1.00 ± 0.05	1.34 ± 0.35	NA
Creatinine (mg/dL; mean ± SD)	0.77 ± 0.19	0.90 ± 0.20	1.18 ± 0.52	<0.001
Creatinine-based eGFR (ml/min per 1.73 m ² ; mean ± SD)	94 ± 23	79 ± 17	62 ± 18	<0.001

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; ACE-I, angiotensin converting enzyme inhibitors; and eGFR, estimated glomerular filtration rate

Table 2

Association of Cystatin C with Sudden Cardiac Death

Measure and Outcome Cystatin C and SCD	Tertile 1	Tertile 2	Tertile 3
Cystatin C (mg/liter)	≤ 0.91	0.92–1.09	≥1.10
Cystatin-based eGFR* (ml/min/1.73m²)	≥86	69–85	≤68
No. of participants	1579	1582	1304
No of SCD events	15	40	36
Hazard Ratio (95% CI)			
Unadjusted	1.00	3.13 (1.67, 5.86)	3.92 (2.05, 7.47)
Adjusted [†]	1.00	2.72 (1.44, 5.16)	2.67 (1.33, 5.35)

* Cystatin based estimated glomerular filtration rate (eGFR) = $76.7 \times \text{cystatin C}^{-1.19}$

[†] Adjusted for age, gender, race, current smoking, alcohol use, LDL, HDL, diabetes, systolic blood pressure, diastolic blood pressure, calcium channel blockers, diuretics, aspirin, left ventricular hypertrophy, physical activity, family history of cardiovascular disease, and myocardial infarction and congestive heart failure as time dependent covariates

Table 3

Association of creatinine-based estimated GFR with Sudden Cardiac Death

Measure and Outcome	Creatinine-based eGFR and SCD	Tertile 1	Tertile 2	Tertile 3
	Range of Values (ml/min/1.73m ²)	≥88	68–87	≤67
No. of participants		1497	1481	1487
No of SCD events		23	31	37
Hazard Ratio (95% CI)				
Unadjusted		1.00	1.55 (0.88, 2.75)	2.00 (1.16, 3.47)
Adjusted*		1.00	1.31 (0.73, 2.36)	1.65 (0.93, 2.94)

* Adjusted for age, gender, race, current smoking, alcohol use, LDL, HDL, diabetes, systolic blood pressure, diastolic blood pressure, calcium channel blockers, diuretics, aspirin, left ventricular hypertrophy, physical activity, family history of cardiovascular disease, and myocardial infarction and congestive heart failure as time dependent covariates